

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/016867 A3

(51) International Patent Classification⁷: C12N 5/00, 5/08, C12Q 1/68, G01N 1/30, 33/48, 33/53, 33/536, 33/543, 33/555, 33/566, 33/567, 33/574

(21) International Application Number: PCT/US02/26811

(22) International Filing Date: 21 August 2002 (21.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/314,188 21 August 2001 (21.08.2001) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): VENTANA, MEDICAL, SYSTEMS, INC [US/US]; 1910 Innovation Park Drive, Trucson, Arizona 85737 (US).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): BACUS, Sarah, S. [US/US]; 1222 Indian Trail, Hinsdale, IL 60521 (US).

(74) Agent: williams, Andrew, W.; MCDONNELL BOEHNEN HULBERT & BERGHOFF, 300 South Wacker Drive, Suit 3200, Chicago, Illinois 60606 (US).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
28 August 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/016867 A3

(54) Title: METHOD AND QUANTIFICATION ASSAY FOR DETERMINING C-KIT/SCF/PAKT STATUS

(57) Abstract: This invention provides methods for determining or predicting response to cancer therapy in an individual using differential image analysis of immunohistochemically stained tumor samples.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/26811

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 5/00, 5/08; C12Q 1/68; G01N 1/30, 33/48, 33/53, 33/536, 33/543, 33/555, 33/566, 33/567, 33/574
 US CL : 435/6, 7.1, , 7.2, 7.23, 7.24, 7.92, 40.5, 40.52, 375; 436/63, 64, 501, 536

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 7.1, , 7.2, 7.23, 7.24, 7.92, 40.5, 40.52, 375; 436/63, 64, 501, 536

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,T	WINTER-VANN AM, et al. Targeting Ras signaling through inhibition of carboxyl methylation: an unexpected property of methotrexate. Proc Natl Acad Sci USA. 27 May 2003, Vol. 100, No. 11, pp. 6529-6534; entire document.	1-11
Y,T	WEST KA, et al. Activation of the PI3K/Akt pathway and chemotherapeutic resistance. Drug Resist Updat. December 2002, vol. 5, No. 6, pp. 234-248; entire document.	12-22
Y,P	RUSNAK DW, et al. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo. Mol Cancer Ther. December 2001, Vol. 1, pp. 85-94; entire document.	23-32
Y,T	DeMatteo RP. The GIST of targeted cancer therapy: a tumor (gastrointestinal stromal tumor), a mutated gene (c-kit), and a molecular inhibitor (STI571). Ann Surg Oncol. November 2002, Vol. 9, No. 9, pp. 831-839; entire document.	12-22
Y,T	STAL O, et al. Akt kinases in breast cancer and the results of adjuvant therapy. Breast Cancer Res. 2003, vol. 5, pp. R37-R44; entire document.	1-11
Y	GLASPY J. Clinical applications of stem cell factor. Curr Opin Hematol. May 1996, vol. 3, No. 3, pp. 223-229; entire document.	1-32



Further documents are listed in the continuation of Box C.



See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 May 2003 (22.05.2003)

Date of mailing of the international search report

24 JUN 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Stephen L. Rawlings, Ph.D.

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

PCT/US02/26811

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KRYSTAL GW, et al. The selective tyrosine kinase inhibitor STI571 inhibits small cell lung cancer growth. Clin Cancer Res. August 2000, Vol. 6, pp. 3319-3326; entire document.	23-32
Y	HASSAN HT, et al. Stem cell factor as a survival and growth factor in human normal and malignant hematopoiesis. Acta Haematol. 1996, Vol. 95, No. 3-4, pp. 257-262; entire document.	1-32
Y	RADOSEVIC N, et al. Cell cycle regulatory protein expression in fresh acute myeloid leukemia cells and after drug exposure. Leukemia. April 2001, vol. 15, No. 4, pp. 559-566; entire document.	12-22
Y,T	NIO Y, et al. Immunohistochemical expression of receptor-tyrosine kinase c-kit protein in invasive ductal carcinoma of the pancreas. Anticancer Drugs. April 2003, vol. 14, No. 4, pp. 313-319; entire document.	1-11
Y	PERTUSSINI E, et al. Investigating the platelet-sparing mechanism of paclitaxel/carboplatin combination therapy. Blood. 01 February 2001, Vol. 97, No. 3, pp. 638-644; entire document.	12-22
Y	KAUSCH C, et al. Effects of troglitazone on cellular differentiation, insulin signaling, and glucose metabolism in cultured human skeletal muscle cells. Biochem Biophys Res Commun. 26 January 2001, Vol. 280, No. 3, pp. 664-674; entire document.	12-22
Y	CIOCCA DR, et al. Molecular markers for predicting response to tamoxifen in breast cancer. Endocrine. August 2000, Vol. 13, No. 1, pp. 1-10; entire document.	12-22
Y,P	BACUS SS, et al. AKT2 is frequently upregulated in HER-2/neu-positive breast cancers and may contribute to tumor aggressiveness by enhancing cell survival. Oncogene. 16 May 2002, Vol. 21, No. 22, pp. 3532-3540; entire document.	1-11
Y	BECK D, et al. Expression of stem cell factor and its receptor by human neuroblastoma cells and tumors. Blood. 15 October 1995, Vol. 86, No. 8, pp. 3132-3138; entire document.	1-32

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/26811

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒
☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/26811

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-11, drawn to a method for assessing a response to an agent following administration of the agent to an individual.

Group II, claim(s) 12-22, drawn to a method for predicting the response to an agent following administration of the agent to an individual.

Group III, claim(s) 23-32, drawn to a method for identifying a compound.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Species A: The method of claims 1, 12, or 23, wherein said biological marker is c-kit.

Species B: The method of claims 1, 12, or 23, wherein said biological marker is SCF.

Species C: The method of claims 1, 12, or 23, wherein said biological marker is pAKT.

Species D: The method of claims 1, 12, or 23, wherein said biological marker is pc-kit.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of group I is measuring the response to administering an agent.

The special technical feature of group II is predicting the response to administering an agent.

The special technical feature of group III is identifying a compound that produces a desired therapeutic response.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The special technical feature of species A is measuring the amount of c-kit.

The special technical feature of species B is measuring the amount of SCF.

The special technical feature of species C is measuring the amount of pAKT.

The special technical feature of species D is measuring the amount of pc-kit.

INTERNATIONAL SEARCH REPORT

PCT/US02/26811

Continuation of B. FIELDS SEARCHED Item 3:

MEDLINE, WEST: Assessment of response to therapy, prediction of response to therapy, evaluation of prognostic value of biomarkers, monitoring therapeutic response, screening to identify therapeutic agents, measuring expression of c-kit, SCF, or AKT, measuring levels of activated c-kit or AKT, ELISA, Western, immunohistochemistry, FACS, immunoprecipitation, tumor-associated antigens, cancer, chemotherapy, image analysis, efficacy, effectiveness.